Process for preparing clopidogrel compositions

This invention relates to pharmaceutical compositions comprising clopidogrel and to processes for preparing such compositions.

Clopidogrel is a known anti-thrombotic agent which inhibits platelet aggregation. See Merck Index, 12th Edition, entry 2457. Clopidogrel is administered currently in the form of the biphosphate salt as a film-coated tablet.

Some clopidogrel salts are known to exhibit difficulties in formulation. The present applicants have found that clopidogrel in base or salt form, e.g. as mesylate or hydrochloride, is problematic to formulate for example as a tablet, and attribute this principally to hygroscopicity. Furthermore, the applicants have found that clopidogrel tablets suffer from degradation on storage.

The present applicants have sought to overcome the problems of hitherto known clopidogrel compositions.

In one aspect, therefore, this invention provides a composition suitable for oral administration comprising clopidogrel in base or pharmaceutically acceptable salt form which composition comprises a polymer coating.

The polymer coating may comprise a polyvinyl acetate or a polyvinyl alcohol.

In this and other aspects of the invention described below, when in salt form clopidogrel may be selected from mesylate, hydroiodide, hydrobromide and hydrochloride.

In another aspect this invention provides a composition suitable for oral administration comprising clopidogrel in base or pharmaceutically acceptable salt form which composition comprises a hydrophobic component.

Suitable hydrophobic components include hydrogenated vegetable oils.

The hydrophobic component-containing compositions of this invention may comprise a polymer coating, e.g. a polyvinyl acetate or a polyvinyl alcohol. In a preferred aspect, the hydrophobic component, when present, is not coated.

In another aspect, this invention provides clopidogrel in form of coated particles, granules or agglomerates.

In a further aspect, this invention provides a composition suitable for oral administration comprising clopidogrel in base or pharmaceutically acceptable salt form wherein the clopidogrel is in the form of coated particles, granules or agglomerates.

In a preferred aspect, this invention provides a composition suitable for oral administration comprising clopidogrel in pharmaceutically acceptable salt form which composition comprises
- a polymer coating selected from a polyvinyl acetate or a polyvinyl alcohol, and
- a hydrophobic component comprising a hydrogenated vegetable oil,
wherein the salt is selected from mesylate, hydrobromide, hydroiodide and hydrochloride, and wherein the clopidogrel is in the form of coated particles, granules or agglomerates.

The particle-, granule- or agglomerate-coating may comprise a hydrophobic polymer, e.g. a polyvinyl acetate or a polyvinyl alcohol, a hydrogenated vegetable oil or a cyclodextrin.

Preferred polymer coatings employed in the compositions of this invention are selected from celluose acetate, polymethacrylates for example Eudragit E or Eudragit NE 30 D, and ethylcellulose.

Suitable vegetable oils include hydrogenated cottonseed oil e.g. those available commercially as Lubritab or Sterotex; hydrogenated palm oil, e.g. available as Softisan 154 or Dynasan P60; hydrogenated soyabean oil such as that available as Sterotex HM.

The hydrophobic component may be selected from cetyl alcohol, cetostearyl alcohol, cholesterol, gyceryl monostearate, glyceryl monooleate, glyceryl palmitostearate and stearic acid.

The cyclodextrin may comprise an alpha-, beta- or gamma-cyclodextrin.

The compositions of this invention herein described may be administered in form of a tablet, sachet, or hard or soft gelatine capsule. Coated tablets are preferred.

In the compositions of the invention, the clopidogrel may be present in an amount of up to 50% by weight, for example 10 to 45%, e.g. 20 to 40%, e.g. 25 to 35% by weight, based on the total weight of the composition.

Thus components of the compositions of this invention may include:

- a sugar, e.g. a lactose, in an amount when present of up to 60% by weight, for example 20 to 50%, e.g. 25 to 40% by weight based on the total weight of the composition. Lactose DCL 11 is a suitable grade in the compositions of this invention;

- a microcrystalline cellulose in an amount when present of up to 40% by weight, for example 5 to 35%, e.g. 8 to 25%, e.g. 10 to 20% by weight based on the total weight of the composition. Avicel PH 112 is an appropriate grade for use in the compositions of this invention;

- a starch in an amount when present of up to 40% by weight, for example 5 to 35%, e.g. 8 to 20%, e.g. 10 to 17% by weight based on the total weight of the composition. Starch 1500 LM is an appropriate grade for use in the compositions of this invention;

- a dessicant for example milled anhydrous silica, available commercially under the trade mark Syloid AL; this component when present may be in an amount of up to 8% by weight of the composition, e.g. 0.5 to 6%, e.g. 1 to 4% by weight;

- the hydrogenated vegetable oil when present in an amount of up to about 15% by weight, e.g. 1 to 10%, e.g. 2 to 7% by weight, based on the weight of the composition. Such oils are commercially available for example under the trade mark Sterotex;

- the polymer coating, when present, in an amount of up to about 10 % by weight, e.g. 2 to 8%, e.g. 4 to 6 % by weight, based on the weight of the composition. Such coatings are available commercially for example under the trade mark Opadry AMB;

- a filler in an amount when present of up to 80% by weight, for example 5 to 75%, e.g. 10 to 65%, e.g. 15 to 50% by weight based on the total weight of the composition. Mannitol and xylitol are examples of suitable fillers in compositions of this invention.

Other components may include titanium dioxide, a hydroxypropyl methylcellulose, a hydroxyl propylcellulose and a propylene glycol.

The compositions of this invention are more straightforward to formulate than hitherto known compositions. The applicants have found that processability of the components in forming, e.g. tablets, is easier than for known processes for making solid clopidogrel compositions.

The compositions of this invention are storage-stable. Thus no or negligible degradation is observed on storage at ambient conditions over periods of days, weeks and months.

The clopidogrel employed in the compositions and processes of this invention may be in racemate form, in form of a partially- or wholly-enriched diastereomer. Thus the clopidogrel may be in form of a pure or substantially pure diastereomer, e.g. > 90% e.g. 93%, 94%, 95% or > 95%, e.g. 96%, 97% or greater diastereomer as determined using known methods.

In another aspect, this invention provides a process for preparing tablets comprising clopidogrel in base or pharmaceutically acceptable salt form which process comprises
a) compacting the clopidrogrel with anhydrous or substantially anhydrous components so as to form aggregates,
b) breaking down the aggregates so as to form granules or particles,
c) optionally mixing the granules or particles with at least one further component, and
d) compacting or compressing the granules or particles thus formed into tablets.

Compaction may be carried out for example using a roller compactor.

The present applicants understand roller compaction to be a form of high-pressure agglomeration. Thus a roller press exerts a mechanical pressure on a powder or other dry bulk material while forced between, for example, two or more counter-rotating rollers. The conditions within the roller compactor are typically such that the material is compressed into compacts which are subsequently passed through a mill to produce granules.

The applicants have found that a Fitzpatrick Chilsonator compactor is a suitable commercially available compactor for roller compaction. Thus the roller speed may be between 1 and 10 rpm, e.g. 2 to 8 such as 3, 4 or 5 r.p.m. Roller pressures applied to the material may be between 300 and 800 pounds per square inch (psi), e.g. 350 (24.60 kg/cm^2) to 700 (49.21 kg/cm^2), such as 500 (35.13 kg/cm^2), 550 or 600 psi.

The desiccant, e.g. anhydrous silica, may be mixed with the aggregates or granules. This improves stability and flow of the processed mixture.

A hydrophobic lubricant, e.g. hydrogenated vegetable oil, may be added. This provides improved stability over that observed using conventional lubricants.

The process may be carried out in a low- or ultra-low humidity environment.

The applicants have found that the compacted blend resulting from process step a) may be milled to granules or particles by screening through a comminuting mill, for example an oscillating granulator, quadrocomill or hammer mill. Thus step b) serves to break the aggregates down in size.

In a preferred aspect, process step b) may be carried out so as to form granules with a small or negligible proportion of particles. Thus the output from step b) may amount to 80% or more granules by weight in a granule/particle mixture, e.g. 85%, 90%, 95% or greater e.g. 98%, 99% or 100% granules.

In a further aspect this invention provides a process for preparing coated clopidogrel particles or granules which process comprises preparing a solution of clopidogrel and the polymer, hydrogenated vegetable oil, or cyclodextrin, in a suitable solvent medium and spray-drying the solution.

The solvent medium may comprise an aqueous or organic solvent or mixture of organic solvents. When an aqueous medium is employed, this may containing up to 100% by weight water, e.g. 5 to 80%, e.g. 10 to 60% by weight.

The thus coated or encapsulated particles or granules may be further processed, for example into tablets using compaction or compression.

Coating of the clopidogrel particles may be achieved using a fluidised bed, e.g. a Wurster, or by water-in-oil or oil-in-water phase separation or coacervation encapsulation methods.

In a further aspect, therefore, coating of the clopidogrel granules or particles may be carried out after process step b) or step c) if present and before step d).

Without being bound to a particular theoretical mechanism of action, the applicants believe that the hydrophobic polymer may establish an effective moisture barrier around the particles or tablets.

Typical dimensions observed using known methods of particles used in this invention range from 50 microns to 150 microns. 75% of the granules of this invention may be in

the size range 100 microns to 500 microns, and 75% of the agglomerates of this invention may be in the size range 500 microns to 2000 microns.

A preferred aspect of the invention is a clopidogrel composition as herein described in form of a coated particle, granule, agglomerate or tablet, wherein the coating is free of or substantially free of HPMC.

Clopidogrel may be administered at a dose of 10mg, 25mg, 50mg, 60 mg, 75mg or 100mg drug substance based on clopidogrel base, depending on the patient's body weight and other circumstances. This dose may be daily. When administered in tablet form, the tablet weight may be for example 50 mg, 100mg, 150 mg, 200 mg or 300 mg in total.

Clopidogrel base, mesylate and hydroiodide are sourced from the Torrent company.

Clopidogrel hydrochloride may be prepared by processes analogous to those disclosed in published patent applications EP 0 281 459 and WO 98/51682.

Clopidogrel hydrobromide may be prepared by passing HBr gas through an organic solution of clopidogrel base, e.g. in toluene, at ambient temperature. Clopidogrel hydrobromide salt precipitates and may be filtered and washed, e.g. with an organic solvent such as toluene. The wet cake of the salt may be dried under vacuum at elevated temperature, for example 50 to 80°C, e.g. 70 to 75°C, to provide clopidogrel HBr as an off-white solid.

In another aspect, this invention provides a composition or process substantially as herein described with reference to the examples. In a further aspect, this invention provides compositions produced using the processes of this invention. The compositions, e.g. tablets, produced by the processes of this invention may be free of or substantially free of HPMC.

Following is a description by way of example only of compositions and processes of this invention.

Example 1

Components	Relative amounts	300 mg tablet
Clopidogrel mesylate	30-32 % w/w of composition	94 mg
Lactose DCL 11	40-50 % w/w of composition	122 mg
Avicel PH 112	10-20 % w/w of composition	30 mg
Starch 1500 LM	10-15 % w/w of composition	30 mg
Syloid AL 1 –FP	1-5 % w/w of composition	12 mg
Sterotex	3-5 % w/w of composition	12 mg

The components (all anhydrous) are mixed together, processed using dry roller compaction into aggregates, compacted to granules and formed into tablets. Processing takes place in a low-humidity environment. 1000 tablets are prepared and divided into 10 lots each of 100 tablets. All ten lots are stored at ambient conditions and inspected at daily intervals.

No degradation is detected by visual inspection after 10 days. Negligible degradation is observed after two months.

Example 2
Example 1 is repeated using clopidogrel hydroiodide in place of the mesylate, using molar equivalent to 75 mg clopidogrel base. Stable tablets are produced.

Example 3
Example 1 is repeated using clopidogrel hydrochloride in place of the mesylate using molar equivalent to 75 mg clopidogrel base. Stable tablets are produced.

Example 4

Components	Relative amounts	300 mg tablet
Clopidogrel mesylate	30-32 % w/w of composition	95 mg
Lactose DCL 11	40-50 % w/w of composition	115 mg
Avicel PH 112	10-20 % w/w of composition	32 mg
Starch 1500 LM	10-15 % w/w of composition	30 mg
Syloid AL 1 –FP	1-5 % w/w of composition	6 mg
Sterotex	3-5 % w/w of composition	10 mg
Opadry AMB	4-6 % w/w of composition	12 mg

The anhydrous components are mixed together, processed in analogous manner to that in Example 1 and formed into tablets. The tablets are coated using Opadry AMB.

1000 tablets are prepared and divided into 10 lots each of 100 tablets. All ten lots are stored at ambient conditions and inspected at daily intervals. No degradation is detected by visual inspection after 10 days. Negligible degradation isobserved after one month.

Example 5
Example 4 is repeated using clopidogrel hydroiodide in place of the mesylate. The molar equivalent to 75 mg clopidogrel base is used. Stable tablets are produced.

Example 6
Example 4 is repeated using clopidogrel hydrochloride (molar equivalent to 75 mg base) in place of the mesylate. Stable tablets are produced.

Compositions containing mannitol as a filler are prepared in the following Examples 7 and 9 to 12.

Examples 7a to c

Components	Mg/tab		
	Example 7 a	Example 7b	Example 7c
Clopidogrel mesylate	99.7	99.7	99.7
Mannitol	106.8	143.8	53.8
Microcrystalline cellulose(Avicel PH 112)	70.5	40.5	115.5
Low substituted hydroxypropyl cellulose (L-HPG 11)	12.0	6.0	20
Polyethylene glycol 6000	6.0	6.0	6.0
Sterotex	5.0	4.0	5.0
Opadry AMB	12.0	12.0	12.0

99.7 mg clopidogrel mesylate are equivalent to 75 mg clopidogrel base.

Composition 7a:
The clopidogrel salt is blended with mannitol, microcrystalline cellulose and part of the low substituted hydroxypropylcellulose. The blend is compacted using a Fitzpatrick Chilsonator roller compactor. The compacts are then milled into granules by screening through an oscillating granulator comminuting mill. The granules are blended with part of microcrystalline cellulose, low substituted hydroxypropylcellulose, mannitol, PEG 6000 and Sterotex. The blend is compressed into tablets using a Korsch rotary compressor. The tablets are then coated with Opadry AMB in a Hicoater perforated coating pan.

An analogous procedure is used to prepare compositions 7b and 7c.

Example 8: Clopidogrel hydrobromide
To a solution of 100 g clopidogrel base in 1000 ml toluene is passed hydrogen bromide gas for 15 minutes at ambient temperature. Clopidogrel HBr precipitates. The precipitated clopidogrel.HBr salt is filtered and washed with 500 ml toluene. The wet cake of the salt is dried under vacuum at 70 to 75°C overnight to give clopidogrel.HBr as an off-white solid.
Yield: 88.1 g (70%)

Examples 9a to c

Components	Mg/tab		
	Example 9a	Example 9b	Example 9c
Clopidogrel hydrobromide	93.9	93.9	93.9
Mannitol	112.6	149.6	59.6
Microcrystalline cellulose(Avicel PH 112)	70.5	40.5	115.5
Low substituted hydroxypropyl cellulose (L-HPC 11)	12.0	6.0	20
Polyethylene glycol 6000	6.0	6.0	6.0
Sterotex	5.0	4.0	5.0
Opdary AMB	12.0	12.0	12.0

93.9 mg clopidogrel hydrobromide are equivalent to 75 mg clopidogrel base. Compositions 9a to 9c are prepared in analogous manner to that for 7a.

Examples 10a to 10c

Components	Mg/tab		
	Example 10a	Example 10b	Example 10c
Clopidogrel hydroiodide	104.9	104.9	104.9
Mannitol	101.7	138.6	48.6
Microcrystalline cellulose(Avicel PH 112)	70.5	40.5	115.5
Low substituted hydroxypropyl cellulose (L-HPC 11)	12.0	6.0	20
Polyethylene glycol 6000	6.0	6.0	6.0
Sterotex	5.0	4.0	5.0
Opadry AMB	12.0	12.0	12.0

104.9 mg clopidogrel hydroiodide are equivalent to 75 mg clopidogrel base. Compositions 10a to 10c are prepared in analogous manner to that for 7a.

Examples 11a to 11c

Components	Mg/tab		
	Example 11a	Example 11b	Example 11c
Clopidogrel hydrochloride	83.5	83.5	83.5
Mannitol	123.0	160	70
Microcrystalline cellulose(Avicel PH 112)	70.5	40.5	115.5
Low substituted hydroxypropyl cellulose (L-HPC 11)	12.0	6.0	20
Polyethylene glycol 6000	6.0	6.0	6.0
Sterotex	5.0	4.0	5.0
Opadry AMB	12.0	12.0	12.0

83.5 mg clopidogrel hydrochloride are equivalent to 75 mg clopidogrel base.
The compositions 11a to 11c are prepared in analogous manner to 7a above.

Examples 12a and 12b: clopidogrel HCl tablets

Components	Mg/tab	
	Example 12a	Example 12b
Clopidogrel hydrochloride (equiv. clopidogrel 75 mg)	83.51	83.51
Mannitol	138	138
Microcrystalline cellulose (Avicel PH 112)	43	43
Low substituted hydroxypropyl cellulose (L-HPC 11)	20	20
Polyethylene glycol 6000	7.5	7.5
Hydrogenated vegetable oil	6	6
Opadry AMB	7.2	
Hydroxypropylmethylcellulose		7.2
Iron oxide red	qs	qs
Titanium dioxide	qs	qs

"qs": quantity sufficient to achieve desired shade or colour

The compositions are prepared in analogous manner to that in Example 7a above, with the omission of Opadry AMB coating in the formulation of Example 12b. The tablet composition of Example 12a exhibits enhanced stability over that of Example 12b.

The process of this invention, including the use of roller compaction, serves to provide more stable and robust clopidogrel compositions than hitherto known compositions. This allows economies such as elimination of more expensive packaging materials. The compositions are reproducible, straightforward and economic to manufacture. In particular the invention provides more stable solid oral dosage forms of clopidogrel-mesylate, -hydroiodide and -hydrochloride.